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A simple formula for quantification and comparison of systemic drug dosage patterns in the context of application times

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Abstract

In order to compare administered drug dosage patterns between different persons or at different times in the same person, a novel formula is proposed that takes into consideration the application times of a specific drug. The herein presented formula permits the calculation of persisting or residual drug activity as related to a time of reference. The obtained value is based on easily available data such as the absolute amount of particularly given drug doses, the patient's body weight and the time frame in which the drug doses were administered. The only genuine pharmacokinetic parameter that has to be considered is the elimination half-life, which is usually available for most drugs from their basic information. The finally resulting figure is called "residual drug activity coefficient" (RDAC), which is a dimensionless unit and specific for each drug. For its rational use further clinical investigations aiming to correlate the spectrum of possible RDAC levels with corresponding clinical effects represent the next step in the use of this mathematical model. *Anestezjologia i Ratownictwo 2013; 7: 401-403*

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When retrospectively analyzing anesthesia records as a usual supervision and evaluation effort during training and education of young colleagues, one often has to estimate whether a certain drug dosage displayed in such a record was adequate in the sense of dosing and times of application (1, 2). This is not at all that trivial as it might appear at the first sight and certainly not an easy undertaking. This shortcoming is based among others on the fact that the analyzing person lacks both, the knowledge about the course of the surgical stimulation, as well as the direct observation of the patient's response to it. Nevertheless, senior anesthetists and personnel with didactic assignments have to do this job in order to draw conclusions about the course and quality of the investigated anesthesia. What can be instantly done without any additional information is to extract from the record the entries for total drug amount in mg per bodyweight in kg per hour. So for example a 3 hours anesthesia in a 70 kg person who received all together 100 mg of atracurium leads to this result: 0.48 mg/kg/h which is certainly a quantitative and comparable result. However, it lacks a fundamental dimension: when and in which partitions has the drug been given during the whole period of that anesthesia and therefore how much of that drug action was still persisting at the end of the procedure? It's obvious that if a larger part of the total amount is given closer towards the end of anesthesia, the more drug activity is persisting (with all negative consequences), without affecting the calculated mg/kg/h value. The elimination of this uncertainty is the scope of this work.In particular in anaesthesia, an extremely important aspect in the assessment of a given drug dosage is the question of residual drug activity at the time of emerging from anesthesia, when nearly all intraoperative administered drugs still exert a certain post-anesthetic activity. This residual drug action can be beneficial as in case of persisting analgesic activity that doesn't preclude sufficient spontaneous respira-

tion. Hereby a more or less wide residual activity window might be ideal, with distinct upper and lower margins. In the case of non-depolarizing muscle relaxants, a residual effect is in no case beneficial and above a certain extent even harmful. It's obvious that non-depolarizing muscle relaxants can be antagonized either by acetylcholine esterase blockers or directly reversed by sugammadex. However, it's a widely accepted attitude to maintain an initial neuromuscular blockade only if it seems necessary for surgical reasons and otherwise to let it decay as soon as possible aiming to have a higher than 0.9 of a train-of-four (TOF)-ratio towards the end of the intervention 3, 4). In an ideal case, the course of the neuromuscular blockade is documented by repeated relaxometric measurements. However, the level of the blockade is not a continuous variable; in many cases it's even not available. That's why finally the person who reads the record only can see the dosing pattern to estimate the adequacy of the administered dosage.For this purpose, an easy to calculate „Residual Drug Activity Coefficient" (RDAC) formula is presented here, which aims to quantify drug dosage by considering the times of applications, either all at once or in partial amounts. To make it clear from the beginning, this formula cannot and doesn't intend to replace careful surveillance of the relaxation grade. Neither is it able to predict drug levels over time. But what it certainly does and what is really new in this respect is its ability to incorporate both, the given drug doses and their timing in a single dimensionless figure that represents the remaining drug activity at a defined time at a "time of reference" (ToR) of choice. To formulate it in a positive way, the RDAC simplifies for the user the estimation of a given drug pattern, thus providing a quantified value for residual drug activity and also enabling comparisons between different drug dosage patterns, especially if multiple doses are given at random time periods. In a further phase of investigations, after having correlated a multitude of RDAC values to matching clinical symptoms (e.g. prevalence of residual block), one eventually would be able to predict certain threshold limits that represent relevant states of neuromuscular transmission.

To explain how the RDAC value is calculated, 2 theoretical examples of non-depolarising relaxant dosing patterns are presented. They have the same total amount of given drug in the same patient during the same time period. The only difference is in the size of the partial dose fragments and their timing. For this reason, we take again a 70 kg patient undergoing an anesthesia for 180 minutes, who receives a total amount of 100 mg atracurium. The only difference between the 2 cases lays in the timing of the partial doses:

- Case A (a typical and seemingly adequate dosing pattern): intubation dose of 50 mg followed by repetition doses of 15 mg after 50 min, 20 mg after 95 min, and finally 15 mg after 130 min.
- Case B (an inadequate dosing pattern for the sake of distinction): intubation dose of 40 mg followed by repetition doses of 10 mg after 100 min, 20 mg after 125 min, and finally 20 mg after 160 min.

Both dosage patterns represent a dosing of 0.48 mg/kg/h, but at first glance one already can expect that in case B a marked residual block may result at the end of anesthesia due to the late administration of rather large subsets.

A quantitative distinction between A and B can be achieved by using this RDAC formula:

$$\textit{Residual drug activity coefficient} = \left(\frac{D1/m}{\Delta T1/HL}\right) + \left(\frac{Dn/m}{\Delta Tn/HL}\right)$$

in which D is the drug amount (in mg), m is the body weight of the patient (in kg), ΔT is the time difference between administration and ToR, and finally HL is the plasma half-life of the involved drug. Each single drug administration is represented by a parenthesis with index numbers (here 1 for the first dose and n for subsequent additional doses). In both cases A and B there are 4 consecutive drug administrations, and therefore the formula encompasses 4 blocks in parenthesis:

$$\textit{Residual drug activity coefficient} = \left(\frac{D1/m}{\Delta T1/HL}\right) + \left(\frac{D2/m}{\Delta T2/HL}\right) + \left(\frac{D3/m}{\Delta T3/HL}\right) + \left(\frac{D4/m}{\Delta T4/HL}\right)$$

The time differences of (ToR – ΔT) can be included as positive numbers and for fractions of an hour is easier to resort to minutes as suitable units. In case A the time differences are in consecutive order ΔT1 = 180 min, ΔT2 = 130 min, ΔT3 = 85 and ΔT4 = 50 min. In case B they are ΔT1 = 180 min, ΔT2 = 80 min, ΔT3 = 55 and ΔT4 = 20 min.

For the plasma half-life of atracurium we assume 25 minutes (3, 4). After inclusion of all variables, the 2 formulas appear like this:

$$\textit{RDAC for A} = \left(\frac{50/70}{180/25}\right) + \left(\frac{15/70}{130/25}\right) + \left(\frac{20/70}{85/25}\right) + \left(\frac{15/70}{50/25}\right)$$

and

$$\textit{RDAC for B} = \left(\frac{40/70}{180/25}\right) + \left(\frac{10/70}{80/25}\right) + \left(\frac{20/70}{55/25}\right) + \left(\frac{20/70}{20/25}\right)$$

After performing all divisions inside the parenthesis, the 2 equations are reduced to simple additions:

RDAC for A = *0.09 + 0.04 + 0.09 + 0.11* = ***0.33***

and

RDAC for B = *0.08 + 0.04 + 0.13 + 0.36* = ***0.61***

The higher result in B represents proportionally the more pronounced residual drug activity in this case. Since bodyweight and half-life are constants in the equation, they can be omitted. In this case other dimensions for RDAC result, but the ratio between A and B remains the same. For the sake of simplicity, the formula also can be simplified to:

$$\textit{Residual drug activity coefficient} = \left(\frac{D1}{\Delta T1}\right) + \left(\frac{Dn}{\Delta Tn}\right)$$

The main limitation of this calculation is that it represents only a surrogate parameter for given drug patterns and in no case it can predict drug levels in any of the relevant body compartments. Also it is unsuitable for drugs with slow release or protracted onset of action, where at least initially the passing time does not translate yet to a pharmacokinetic decay in drug activity. On the positive side we have certain benefits: RDAC is sensitive to the timing inside of an assessed drug pattern and needs no further information than the separate doses and their times of application. With this one has an easily accessible tool to compare drug dosing patterns. As soon as certain RDAC levels can be correlated to specific clinical effects, one can use it even to roughly estimate the activity of a given drug in the context of time.

Conflict of interest
The author declares to have no conflicts of interest.

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